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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/594,962

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Tomoki Todo

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EXAMINER

HAMA, JOANNE

ART UNIT

PAPER NUMBER

1632

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/594,962	Applicant(s) TODO ET AL.	
	Examiner JOANNE HAMA	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 5-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/29/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Application is a 37 of PCT/JP05/06396, filed March 31, 2005 and claims priority to foreign application 2004-105273, filed March 31, 2004 in Japan.

Claims 1-20 are pending.

Claims 5-20 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits. Claims 5-20 are withdrawn.

Claims 1-4 are under consideration.

Information Disclosure Statement

Applicant filed an Information Disclosure Statement (IDS) on September 29, 2006. The IDS has been considered.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claim 1-4 are objected to because of the following informalities: claim 1 uses the phrase, "FRP site." This appears to be a typographical error of "FRT site." Appropriate

correction is required. Claims 2-4 are included in the objection because they depend on claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiocca et al., US Patent Application Publication US 2002/0110543 A1, published August 15, 2002, in view of Buchholz et al., 2001, Nature Biotechnology, 19: 1047-1052, Krisky et al., 1998, Gene Therapy, 5: 1517-1530.

Chiocca et al., in Example 2, teach Herpes simplex virus type-1 (HSV-1) mutants lacking the UL39 (encoding ribonucleotide reductase, ICP6) and both copies of the γ 34.5 gene (e.g., MGH1, G207) and show oncolytic effects as well as potent immunizing effects. Chiocca et al. teach a quick, simple, and efficient system for the generation of oncolytic HSV-1 vectors (designated as the "HSVQuik system"). See, FIG. 7. This system consists of two components: a bacterial artificial chromosome (BAC) clone containing the backbone HSV-I sequence (fHSVQuik-1, about 160 kb); and a transgene-transfer plasmid (pTransfer, 2 kb). HSVQuik takes advantages of the two different site-specific recombination systems, Cre-loxP and Flp-FRT. The fHSVQuik-1 contains a circular form of the HSV-1 genome with deletions in the UL39

gene and both copies of the γ 34.5 gene (derived from the MGH-1). The BAC backbone of the plasmid is inserted at the deleted UL39 locus, flanked by a loxP site and a FRT site, and contains a copy of the red fluorescent protein (RFP) gene as an indicator of the BAC backbone. The BAC backbone also carries the chloramphenicol-resistance gene (Cmr). In addition, the EGFP gene was inserted in frame downstream from the remaining UL39 coding sequence, so that it expresses an ICP6 (AC)-EGFP fusion protein under control of the ICP6 promoter. The plasmid, pTransfer, is a replication-conditional plasmid (R6K gamma-based) and contains a multiple cloning site (MCS) flanked by a loxP site and a FRT site.

First, a series of transfer plasmids were constructed containing one or more transgene cassettes of interest. A transgene cassette of interest (X) was cloned into the MCS of pTransfer. Then, the entire transfer plasmid was inserted into the UL39 locus of the fHSVQuik-1 through Flp-mediated site-specific recombination in *E. coli*. The efficiency of obtaining correct co-integrates is high (up to 80% of the obtained clones possess the expected restriction enzyme-HindIII-pattern; see, FIG. 9) and the procedure is rapid. The resulting HSV-1 precursor BAC clones can be stored as bacterial stocks for further modifications and the BAC DNA can easily be purified by conventional alkaline methods. When the HSV-1 precursor DNA and a Cre recombinase-expressing plasmid were cotransfected into VERO cells, the prokaryotic backbone of the precursor was excised out through recombination of the two loxP sites and the viral genome containing the transgenes of interest was released. Indeed, after a single round of limited dilution of progeny viruses, a number

of clones with GFP but without RFP were obtained. The loss of RFP expression can be used as an indicator for successful removal of BAC backbone. See, FIG. 10.

Further analyses by PCR confirmed the correct genetic identities of the progeny viruses. See, FIG. 11. Characterization of rHsvQ1 by a one-step growth curve, in vivo safety study on BALB/c mice, and cytopathic effect in vitro, are presented in FIG. 12. HSVQuik will allow the rapid and high throughput generation of complex oncolytic viruses for cancer therapy, or other uses, in approximately 2-3 weeks.

With regard to the method being carried out in "liquid phase" (claim 2), it is not entirely clear what this phrase means. The Examiner has looked through the specification for guidance as to what this embodiment was defined as, and could not find any guidance. As such, the Examiner interpreted the phrase to mean that the cre recombinase step was carried out in liquid culture. According to the art, expressing Cre recombinase in liquid culture to effect recombination between two lox sites was known at the time of filing (Buchholz et al., page 1047, 2nd col., parag. under "Directed evolution of recombinases recognizing loxH sites").

It is noted that claim 1 indicates that the herpes virus is inserted into the BAC vector mediated by the cre/lox system, while Chiocca et al. teach the flp/frt system. Removal of bacterial sequence is mediated by flp/frt in the instant application, while Chiocca et al. use cre/lox. The use of the cre/lox system versus the flp/frt is a matter of design choice because both systems are site-specific recombinases and both will accomplish the same biological function, Chiocca et al., page 5, parag. 41.

With regard to the claims being drawn to the deletion or inactivation of ICP47, Krisky et al. teach that deletion of ICP47 will restore normal MHC class I expression and enhance the effectiveness of transgenes designed to increase tumor immunity (Krisky et al., page 1518, 1st parag., 2nd parag.). As such, an artisan would want to include a step of deleting or inactivating ICP47 in order to use the herpes virus in cancer therapy.

Thus, the claims are obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

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/Joanne Hama/
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